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Review Article

TERLIPRESSIN COMBINED WITH NOREPINEPHRINE IN THE TREATMENT OF SEPTIC SHOCK: A SYSTEMATIC REVIEW

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ABSTRACT—**Objective:** The objective of this study was to provide an in-depth analysis of the advantages and potential research directions concerning the utilization of terlipressin (TP) in combination with norepinephrine (NE) for the management of septic shock. **Methods:** A systematic search was conducted across five major electronic databases, namely, PubMed, Cochrane, Embase, ScienceDirect, and MEDLINE, using the Boolean method. The search encompassed articles published until May 22, 2023. Randomized controlled trials investigating the efficacy of TP combined with NE in the treatment of patients with septic shock were considered for inclusion. **Results:** A total of seven trials met the inclusion criteria. The combination therapy of TP and NE exhibited potential benefits in the treatment of adult patients suffering from septic shock. Furthermore, the concurrent administration of TP with NE demonstrated improvements in cardiac output and central venous pressure. However, it is important to acknowledge the presence of certain risks and potential adverse events, including an elevated risk of peripheral ischemia. **Conclusions:** The available evidence supports the notion that early combination therapy involving NE and TP holds promise in terms of reducing the required dosage of NE, enhancing renal perfusion, and improving microcirculation in patients diagnosed with septic shock.

KEYWORDS—Septic shock; terlipressin; noradrenaline; MAP; renal perfusion; microcirculation

ABBREVIATIONS—NE—norepinephrine; TP—terlipressin; $ScvO_2$—central venous oxygen saturation; RCT—randomized controlled trial; CO—cardiac output; SvO_2—mixed venous oxygen saturation; CI—cardiac index; HR—heart rate; ICU—intensive care unit; Lac—lactate; AST—aspartate aminotransferase; CVP—central venous pressure; SV—stroke volume; AKI—acute kidney injury

INTRODUCTION

Septic shock represents an acute and severe manifestation of sepsis, which continues to be a leading cause of mortality in the intensive care unit despite significant advancements in the field of medicine (1–3). In addition to crucial interventions such as fluid resuscitation and antibiotic therapy (4), the recently published Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021 recommend norepinephrine (NE) as the preferred vasoactive agent for patients suffering from septic shock (5). Furthermore, in cases where NE administration reaches its loading dose limit, the guidelines endorse the adjunctive use of vasopressin. Terlipressin (TP), a vasopressin analog, has gained approval for use across a broad range of medical domains, and health care practitioners have accumulated substantial expertise in its administration. Consequently, the combination of TP with NE represents a promising and viable approach for managing septic shock. However, to date, no systematic review has been conducted to examine the efficacy and safety of TP in combination with NE for treating septic shock. Hence, the objectives of this study are to explore the optimal regimen for TP combined with NE in septic shock treatment, assess the clinical advantages of this combination compared with NE monotherapy, and identify future research avenues.

The primary goals of this investigation are to comprehensively search major medical databases, compile a comprehensive list of relevant clinical trials investigating the use of TP combined with NE in septic shock treatment, and conduct a comparative analysis of these studies while evaluating the potential risk of bias. By undertaking this systematic review, we aimed to elucidate the strengths and limitations associated with TP combined with NE based on the existing body of research and subsequently outline the future directions that should be pursued in this field.

MATERIALS AND METHODS:

Systematic review approach

A systematic review was conducted by two independent reviewers (F.M., L.L.) to assess whether the combination of TP and NE yields superior outcomes, including reduced 28-day mortality, improved renal perfusion, and enhanced microcirculation when compared with the use of NE alone in patients diagnosed with septic shock. The methodology used in this review adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (6,7).

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Clinical questions

This review aimed to address the following clinical questions regarding the treatment of septic shock:

Does the combination therapy of TP and NE confer greater clinical benefits in patients with septic shock?
Are there notable improvements in 28-day mortality rates, renal perfusion, and microcirculation when using the combination of TP and NE in patients with septic shock?

LITERATURE SEARCH

To ensure a comprehensive analysis, a systematic search was conducted across five prominent electronic databases, namely, PubMed, Cochrane, Embase, ScienceDirect, and MEDLINE. The search was performed using the Boolean method, and the specific search strategies used for each database are detailed in Table 1. The search encompassed articles published until May 22, 2023. The key search terms used were "septic shock" and "TP." The primary focus was on identifying randomized controlled trials investigating the use of TP in combination with NE for the treatment of patients with septic shock.

STUDY SELECTION

During the study selection process, any disagreements among the reviewers were resolved through discussion. Duplicate publications were removed, and the remaining articles were screened based on their titles and abstracts. The inclusion and exclusion criteria outlined hereinafter were applied to identify relevant literature for this review:

Inclusion criteria

1. Studies involving adult patients or animals with a confirmed diagnosis of septic shock
2. Availability of complete data on primary and secondary outcomes for all participants
3. The experimental group receiving treatment with TP and NE, while the control group receiving NE alone
4. Availability of the full text of the study
5. Studies written in English
6. Selection of studies published within the past 15 years

Exclusion criteria

1. Studies consisting solely of reviews, editorials, letters, or abstracts
2. Studies comparing TP alone with NE

DATA EXTRACTION

The following data were extracted from the selected studies: publication author, study subjects, control group characteristics, experimental group characteristics, primary outcome measures, secondary outcome measures, timing and dosage of TP administration, control group treatment regimen, type and method of TP measurement, and summary of conclusions. Independent investigators (F.M., L.L.) performed the data extraction.

NARRATIVE SYNTHESIS

Because of the heterogeneity observed among the included studies, it was not feasible to conduct a formal meta-analysis. Consequently, a comprehensive qualitative review of the available

TABLE 1. **Specific search strategies**

Database	Strategy	No. results before inclusion/ exclusion criteria
PubMed, PubMed Central (PMC), Medline	"Shock, Septic" OR "Septic shock" OR "Toxic-shock syndrome" OR "Septic Shock" OR "septic shock" OR "toxic shock syndromes" OR "Shock, Septic" OR "Shock, Toxic" OR "Toxic Shock Syndrome" OR "Shock Syndrome, Toxic" OR "Toxic Shock Syndromes" OR "Toxic Shock" OR "Shock, Endotoxic" OR "Endotoxin Shock" OR "Endotoxin Shocks" OR "Shock, Endotoxin" OR "Shocks, Endotoxin" AND "Terlipressin" OR "Glycylpressin" OR "TGLVP" OR "terlipressin" OR "Triglycyl Lysine Vasopressin" OR "Triglycylvasopressin" OR "glypressin" OR "Glypressin" OR "Triglycyl-(8-lysine)vasopressin" OR "Remestyp"	140
Embase	"shock, septic" OR "septic shock" OR "toxic-shock syndrome" OR "toxic shock syndromes" OR "shock, toxic" OR "shock, endotoxic" OR "endotoxin shock" OR "endotoxin shocks" OR "septic shock" AND "terlipressin" OR terlipressin OR glycylpressin OR tglvp OR terlipressin OR "triglycyl lysine vasopressin" OR triglycylvasopressin OR glypressin OR triglycyl- AND "8lysine" AND vasopressin OR remestyp OR "terlipressin"	382
Cochrane	"Terlipressin," "Glycylpressin," "TGLVP," "terlipressin" OR "Triglycyl Lysine Vasopressin" OR "glypressin" OR "Glypressin" OR "Remestyp" AND "Shock, Septic" OR "Septic shock" OR "Toxic-shock syndrome" OR "Septic Shock" OR "septic shock" OR "toxic shock syndromes" OR "Shock, Septic" OR "Shock, Toxic" OR "Toxic Shock Syndrome" OR "Shock Syndrome, Toxic" OR "Toxic Shock Syndromes" OR "Toxic Shock" OR "Shock, Endotoxic" OR "Endotoxin Shock" OR "Endotoxin Shocks" OR "Shock, Endotoxin" OR "Shocks, Endotoxin"	69
Science direct	"Terlipressin" OR "Glycylpressin" OR "TGLVP" OR "terlipressin" AND "Shock, Septic" OR "Septic shock" OR "Toxic-shock syndrome" OR "Septic Shock"	27

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literature was conducted, aiming to provide a narrative synthesis of the findings.

QUALITY ASSESSMENT/RISK OF BIAS ASSESSMENT

The risk of bias for the included studies was assessed using the Cochrane Collaboration tool (8). The assessment considered the following domains: random sequence generation, allocation concealment, blinding of subjects and staff, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain of each study was evaluated, and judgments of "low," "unclear," or "high" risk of bias were assigned accordingly. Studies that demonstrated a low risk of bias across all domains were classified as having a low risk of bias, whereas those with a high risk of bias in one or more domains were deemed to have a high risk of bias. Implementation bias and detection bias were independently assessed by two authors, with any discrepancies resolved through discussion. The results of the bias assessment are presented in Figure 1.

RESULTS

A total of 618 articles were initially screened. After reviewing the titles and abstracts, 473 articles were deemed irrelevant and subsequently excluded. Among the remaining 145 full-text articles, 138 were further excluded based on the inclusion and exclusion criteria. Ultimately, a total of seven studies were included in this systematic review. The detailed screening process is illustrated in Figure 2. Basic information and outcomes of the included studies can be found in Table 2, whereas Table 3 provides a comparison of medication timing and dosage across the included studies. The results of the included publications are summarized in Table 4.

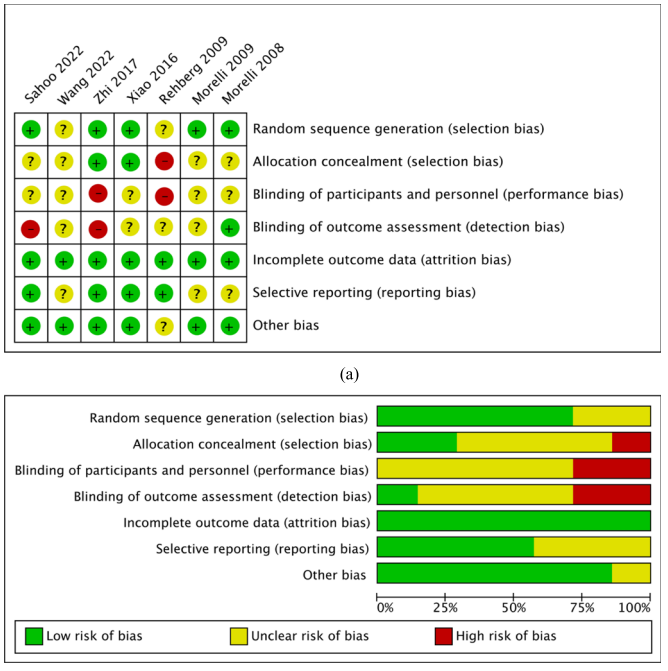

FIG. 1. **A, Risk of bias summary**. B, Risk of bias graph. Risk of bias assessment: overall risk of bias for all included trials.

Qualitative synthesis findings

Timing, duration, and dosage of TP

Among the seven studies included in the qualitative synthesis, only one group initiated the use of TP after the NE dosage reached 0.9 μg/kg/min, whereas the remaining groups administered TP immediately upon enrollment. Regarding dosage, only one group received a 1-mg injection, whereas the remaining five groups were administered doses ranging from 1 to 1.3 μg/kg/h. It is worth noting that one group experienced substantial dosage fluctuations, ranging from 0.6 to 2.4 μg/kg/h. Regrettably, of the six studies that continued TP administration, only two studies imposed limitations on the duration of the infusion, specifically 12 and 24 h, respectively.

Primary outcome

Among the seven included studies, both the TP + NE group and the NE group achieved the targeted MAP range. In six studies, it was observed that NE consumption decreased in the TP + NE group, whereas one study did not provide an explanation regarding NE consumption. Five studies demonstrated an increase in urine volume in the TP + NE group, whereas one study indicated a decrease in creatinine levels, and the remaining study found no significant difference between the two groups. Four studies showed a greater decline in lactate levels in the TP + NE group, whereas the remaining three studies either showed no significant difference or did not report this indicator. Three studies reported lower heart rate (HR) in the TP + NE group, whereas the remaining four studies found no significant difference or did not include this indicator.

Secondary outcome

Analysis of the secondary outcomes in the seven included studies focused on the following aspects:

1. Hemodynamics and blood flow velocity: Some studies suggested that, compared with the NE group, the TP + NE group exhibited a decrease in central venous pressure, an increase in stroke output, a decrease in cardiac index, a reduction in radial artery diameter, and an increase in radial blood flow velocity.
2. Volume balance: Two studies indicated that the TP + NE group required lower volumes of fluid resuscitation compared with the NE group.
3. Oxygen delivery: After 6 h of treatment, one study showed higher $ScvO_2$ levels in the TP + NE group compared with the NE group.
4. Other laboratory-related indicators: One study reported lower creatinine levels and a decreased probability of acute kidney injury in the TP + NE group, along with a lower rate of renal reperfusion therapy.
5. Prognosis: Three studies found no significant difference in the 28-day survival rate, length of intensive care unit stay, and duration of mechanical ventilation between the two groups, whereas one study suggested a higher 7-day survival rate in the TP + NE group.
6. Adverse effects: Two studies indicated a higher likelihood of peripheral ischemia of the limbs in the TP + NE group, and one study reported cases of hyponatremia.

DISCUSSION

The mechanism of action of TP and its association with septic shock

TP is a propeptide derivative of lysine vasopressin and shares a similar physiological role to arginine vasopressin (9,15). Upon

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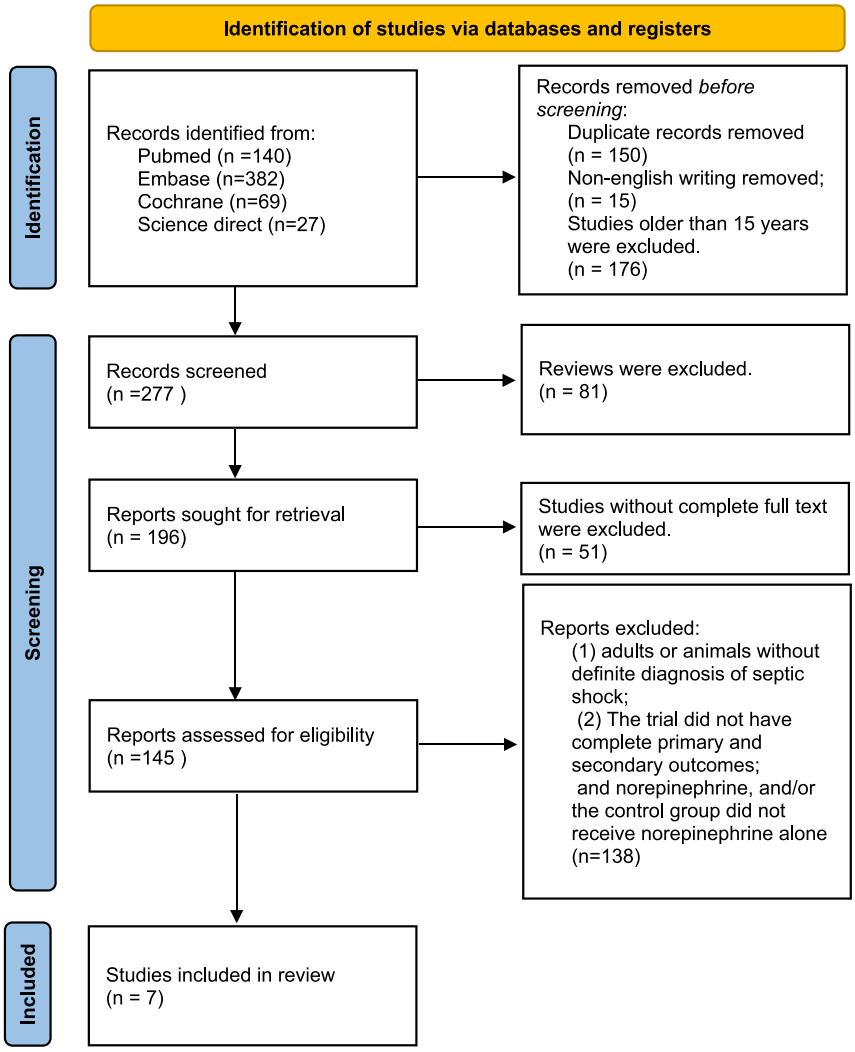
Identification of studies via databases and registers
Identification
Records identified from:
Pubmed (n =140)
Embase (n=382)
Cochrane (n=69)
Science direct (n=27)
Records removed *before screening*:
Duplicate records removed (n = 150)
Non-english writing removed; (n = 15)
Studies older than 15 years were excluded. (n = 176)
Screening
Records screened (n =277)
Reviews were excluded. (n = 81)
Reports sought for retrieval (n = 196)
Studies without complete full text were excluded. (n = 51)
Reports assessed for eligibility (n =145)
Reports excluded:
(1) adults or animals without definite diagnosis of septic shock;
(2) The trial did not have complete primary and secondary outcomes;
and norepinephrine, and/or the control group did not receive norepinephrine alone (n=138)
Included
Studies included in review (n = 7)

Fig. 2. **PRISMA flow diagram.** PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

exposure to endothelin, three residues are cleaved from TP, leading to the formation of lysine vasopressin (10,11). TP primarily acts on V1 receptors in vascular smooth muscle cells and V2 receptors in renal collecting duct cells. When TP binds to the V1 receptor, it induces vasoconstriction and increases blood pressure by causing contraction of vascular smooth muscle cells. On the

Table 2. **Basic information and outcomes of the included studies**

Reference	Study design	Subject of study	Control group	Experimental group	Primary outcomes	Secondary outcomes
Morelli et al. 2008 (25)	RCT	40 adults patients with septic shock	NE (20)	NE + TP (20)	MAP, NE dosage, urine volume	SvO_2, CI, peripheral ischemia of the limbs
Morelli et al. 2009 (9)	RCT	30 adults patients with septic shock	NE (15)	NE + TP (15)	MAP, NE dosage, HR	28-d mortality rate, duration of ICU hospitalization, creatinine levels, proportion of renal replacement therapy utilization
Rehberg et al. 2009 (10)	RCT	18 sheep with septic shock	NE (8)	NE + TP (15)	MAP, NE dosage, HR, Lac	The dosage of fluid resuscitation, AST levels, 28-d mortality rate
Xiao et al. 2016 (11)	RCT	32 adults patients with septic shock	NE (17)	NE + TP (15)	MAP, NE dosage, urine volume, Lac	Radial artery diameter, blood flow velocity, $ScvO_2$ (at 6 h), 7-d survival rate
Zhi et al. 2017 (12)	RCT	57 adult patients with septic shock and ARDS	NE (26)	NE + TP (31)	MAP, HR, urine volume	CVP, volume responsiveness, 28-d survival rate, duration of mechanical ventilation, length of ICU stay
Pallavi et al. 2022 (13)	RCT	50 adults patients with septic shock	NE (25)	NE + TP (25)	MAP, NE dosage, urine volume, Lac	Peripheral ischemia of the limbs, 28-d survival rate
Wang et al. 2022 (14)	RCT	22 adults patients with septic shock	NE (12)	NE + TP (10)	MAP, NE dosage, HR, Lac	Probability of developing AKI, SV

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CI, cardiac index; CVP, central venous pressure; HR, heart rate; ICU, intensive care unit; Lac, lactate; NE, norepinephrine; RCT, randomized controlled trial; $ScvO_2$, central venous oxygen saturation; SV, stroke volume; SvO_2, mixed venous oxygen saturation; TP, terlipressin.

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other hand, when TP binds to the V2 receptor, it enhances the water reabsorption capability of the renal collecting duct cells, thereby exerting an antidiuretic effect. It is worth noting that TP exhibits a greater selectivity for V1 receptors compared with V2 receptors (12,13). The activation of both V1 and V2 receptors by TP allows for simultaneous vasoconstrictor and antidiuretic effects to occur (16,17).

Sepsis and septic shock are global medical challenges, affecting millions of individuals worldwide each year and resulting in significant mortality rates, ranging from one-third to one-sixth of patients (4). Sepsis is characterized by life-threatening organ dysfunction caused by an uncontrolled host response to infection (18). Septic shock refers to a subset of sepsis where circulatory, cellular, and metabolic abnormalities pose a higher risk of mortality compared with sepsis alone. The pathogenesis of septic shock involves intricate physiological processes, including infection, inflammatory response, endothelial cell injury, disrupted blood coagulation, microvascular dysfunction, and tissue and organ damage. These processes interact, giving rise to systemic inflammatory responses, tissue damage, and eventual progression to shock and organ failure (19,20).

The use of vasoactive agents is crucial in the management of patients with septic shock. Among vasoactive agents, NE is typically preferred. However, in recent years, there has been a growing recognition of patients who exhibit decreased sensitivity to catecholamines, necessitating alternative vasopressor agents for their survival (21).

Coadministration of TP and NE: timing, dosage, and duration

In regard to the timing of TP administration, six of the included studies administered TP at the initiation of the study, whereas one study introduced TP after the onset of NE resistance. Regarding the dosage, only one group received a 1-mg bolus, whereas the remaining five groups received doses ranging from 1 to 1.3 μg/kg/h. It is important to note that the discussion of TP dosage and timing should be considered in conjunction.

First, regarding the dosage of TP, preliminary experiments conducted on septic shock–induced rats or rabbits have indicated that the coadministration of TP and NE at lower doses can enhance Rho kinase activity and calcium sensitivity. This combination has demonstrated the ability to improve vascular reactivity and enhance survival rates in these animal models (22).

TABLE 4. **Summary of the results from the included publications**

Reference	Summary of conclusions
Morelli et al. (25)	High-dose TP combined with NE resulted in decreased NE dosage, increased urine volume, and decreased CI and SvO_2. However, patients experienced adverse events such as extremity ischemia and hyponatremia.
Morelli et al. 2009 (9)	Low-dose TP combined with NE resulted in decreased NE dosage, HR, lactic acid, and creatinine levels. The proportion of renal replacement therapy decreased. However, there were no significant differences in 28-d mortality and length of ICU stay.
Rehberg et al. 2009 (10)	Low-dose TP combined with NE decreased NE dosage, HR, and liquid resuscitation dose. However, increased AST levels did not significantly affect 28-d mortality.
Xiao et al. 2016 (11)	Low-dose TP combined with NE reduced NE dosage, increased urine volume, decreased lactic acid, decreased radial artery diameter, increased blood flow velocity, elevated $ScvO_2$, and improved 7-d survival rate compared with NE alone.
Zhi et al. 2017 (12)	Low-dose TP combined with NE increased urine volume and decreased fluid resuscitation dose compared with NE alone. No significant changes were observed in HR, CVP, 28-d mortality, mechanical ventilation time, or ICU stay time.
Pallavi et al. 2022 (13)	Low-dose TP combined with NE decreased NE dosage, increased urine volume, and reduced lactic acid levels. However, patients experienced terminal ischemia of extremities, and the 28-d survival rate did not significantly improve.
Wang et al. 2022 (14)	Low-dose TP combined with NE resulted in decreased NE dosage and HR, increased urine volume, increased SV, and a nonsignificant 20% reduction in the probability of AKI ($P > 0.05$) compared with the NE group.

AKI, acute kidney injury; AST, aspartate aminotransferase; CI, cardiac index; CVP, central venous pressure; HR, heart rate; ICU, intensive care unit; Lac, lactate; NE, norepinephrine; RCT, randomized controlled trial; $ScvO_2$, central venous oxygen saturation; SV, stroke volume; SvO_2, mixed venous oxygen saturation; TP, terlipressin.

TABLE 3. **Comparison of medication time and dose in the included studies**

Reference	Timing of TP use	Measurement of TP used	Type and measurement of drug administration in the control group
Morelli et al. (25)	Once the dose of norepinephrine is reduced to 0.9 μg/kg/min, terlipressin infusion can be initiated.	A single intravenous injection of terlipressin 1 mg	Using NE to maintain the MAP ≥65 mm Hg but ≤75 mm Hg
Morelli et al. 2009 (9)	TP was given immediately after enrollment. Duration was unknown.	Continuous TP infusion of 1.3 μg/kg/h	Using NE to maintain the MAP ≥65 mm Hg but ≤75 mm Hg
Rehberg et al. 2009 (10)	TP was given immediately after enrollment. Duration was unknown.	continuous TP infusion of 1 μg/kg/h	Using NE to maintain the MAP ≥65 mm Hg
Xiao et al. 2016 (11)	TP was given immediately after enrollment. Duration was unknown.	Continuous TP infusion of 1.3 μg/kg/h	Using NE to maintain the MAP ≥65 mm Hg but ≤95 mm Hg
Zhi et al. 2017 (12)	TP was given immediately after enrollment. Duration was unknown.	Continuous TP infusion of 0.6–2.4 μg/kg/h	Using NE to maintain the MAP ≥65 mm Hg but ≤70 mm Hg
Pallavi et al. 2022 (13)	TP was given immediately after enrollment. Continue medication for 12 h.	Continuous TP infusion of 1.2 μg/kg/h	Using NE to maintain the MAP ≥65 mm Hg
Wang et al. 2022 (14)	TP was given immediately after enrollment. Continue medication for 24 h.	Continuous TP infusion of 1.3 μg/kg/h	Using NE to maintain the MAP ≥65 mm Hg

NE, norepinephrine; TP, terlipressin.

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With respect to the timing of TP use, if TP is administered subsequent to high-dose NE administration, the increased oxygen consumption of cells induced by high-dose NE may lead to abnormal glucose metabolism and negative nitrogen balance (23). Consequently, this can significantly diminish the therapeutic efficacy of vasoactive medications. In such circumstances, larger doses of TP and an increased occurrence of TP-related adverse effects may be required. Several studies have indicated that the early initiation of TP treatment can potentially enhance the prognosis of patients with sepsis (24,25).

Regrettably, an insufficient number of clinical trials have documented the duration of intravenous infusion for TP. Among the included studies, only two reported the effects of intravenous infusion at 12 and 24 h, respectively. Our team hypothesizes that the withdrawal of medication may have occurred because of an improvement in the patient's condition. However, the relationship between the duration of TP infusion and different clinical outcomes remains unclear, necessitating further clinical trials to establish definitive evidence.

In the years preceding the introduction of TP, single agents were commonly used to maintain MAP in patients. However, a multicenter study revealed that TP used as the sole vasoactive drug, when compared with NE, effectively increased blood pressure but did not improve the 28-day mortality rate. Furthermore, the probability of experiencing adverse reactions was higher (26,27). Does this imply that TP is ineffective? Clearly, that is not the case. Numerous previous studies have demonstrated that TP usage can enhance renal function, increase urine output, and reduce HR. Although adverse reactions such as limb ischemia and hyponatremia may occur, they are typically associated with high doses of TP (26,28). Hence, using NE as the primary vasopressor alongside adjunctive TP usage not only helps mitigate the adverse effects associated with high-dose TP but also brings about superior clinical benefits for patients.

In conclusion, our team recommends the early combination of low-dose TP with NE for the treatment of septic shock in patients. This approach represents the recommended use of TP in this context, based on the current understanding of its therapeutic effects.

The effect of combining TP with NE on the primary clinical outcome

The impact of TP in conjunction with NE on MAP, HR, and lactic acid levels

In the seven studies we included in our analysis, it becomes evident that all experimental groups receiving TP in combination with NE were able to achieve the predetermined target MAP for maintaining adequate organ perfusion in patients with septic shock. Notably, the TP + NE group demonstrated a faster attainment of the target MAP, which could be attributed to its effects on HR and lactic acid levels.

First, lactic acid serves as a marker reflecting the overall body perfusion (29,30). The administration of TP + NE allows for a quicker achievement of the target MAP, thereby reducing the duration of hypoperfusion in the body. In addition, the rapid increase in blood pressure associated with TP + NE administration triggers a negative feedback response from the pressure sensors located in the carotid sinus, resulting in a decrease in HR (31).

The impact of combining TP with NE on the dosage of NE

Based on the screened articles, six studies have demonstrated that the use of TP in combination with NE can lead to a reduction in the dosage of NE. We believe that the decrease in NE dosage can be attributed to the following reasons.

The potential underlying reasons for the observed reduction in NE dosage can be attributed to the following factors:

1. Synergistic effect: TP and NE exert their effects through different mechanisms of action. TP primarily acts as a vasoconstrictor by stimulating the V1 receptor on vascular epithelial cells (12,13). On the other hand, NE increases cardiac contractility and HR and induces vasoconstriction by stimulating adrenergic receptors (32), When these two agents are combined, their effects on raising blood pressure are mutually enhanced through a synergistic effect. This allows for a reduction in the dosage of NE when used as a standalone agent.
2. Inhibition of NO synthesis: TP, upon stimulation of V1 receptors on vascular endothelial cells, inhibits the synthesis of NO synthase, thereby reducing the release of NO (33,34). NO is a potent vasodilator, and by reducing its levels, the sensitivity of patients with septic shock to catecholaminergic agents is enhanced. Consequently, lower doses of NE are required. Conversely, higher levels of NE are associated with adverse effects such as tachycardia, arrhythmias, intolerance of enteral nutrition, and decreased 30-day survival (35–37).

Therefore, for patients with septic shock, the combination of TP and NE can effectively reduce the dosage of NE, leading to improved clinical outcomes and benefits for the patients.

The effect of TP in combination with NE on secondary clinical outcomes

Effect of TP on renal function

The present study unequivocally demonstrates that the combination of TP and NE leads to improved renal function in patients with septic shock. Importantly, this beneficial effect was observed not only with the combination therapy but also with TP alone, when compared with NE. Liu et al. (26) provided evidence of the TP group experiencing a greater reduction in serum creatinine levels at days 5 and 7 after randomization. Similarly, in a study conducted by Huang et al. (38), which encompassed nine studies involving 850 subjects, TP was found to improve renal function. The analysis revealed a significant decrease in creatinine levels among patients receiving TP therapy compared with those treated solely with catecholamines (standard mean difference, −0.65; 95% confidence interval, −1.09 to −0.22; $P = 0.003$). Furthermore, the study by Wang et al. (14) not only demonstrated the enhancement of renal perfusion through the combination therapy but also used the maximum echo intensity of the contrast agent to reflect renal perfusion via peak ultrasound signal intensity from enhanced renal contrast agent ultrasound. This measurement provided a more intuitive indication of the renal benefits conferred by the drug.

Effect of TP combined with NE in terms of fluid resuscitation

Basic studies have demonstrated that the administration of TP at appropriate concentrations leads to increased blood flow in the mesenteric veins and improved fluid responsiveness in mice with sepsis compared with untreated mice (39).

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The enhancement of fluid responsiveness holds promise for certain clinical conditions that require resuscitation but cannot tolerate large volumes of fluid, such as acute respiratory distress syndrome and liver cirrhosis. In these conditions, where the use of large fluid doses may be problematic, the ability of TP in combination with NE to improve fluid responsiveness offers hope for effective resuscitation strategies.

By using TP alongside NE, clinicians may have an alternative approach to fluid resuscitation in these specific clinical diseases, providing a potential solution where large fluid volumes are not feasible or appropriate.

Additional benefits of TP

Furthermore, aside from the aforementioned studies, the combined use of TP and NE in the treatment of septic shock has been suggested to have an impact on microcirculation perfusion. Morelli et al. (40–42) proposed that TP contributed to hemodynamic stabilization while reducing the requirement for NE. In addition, they observed an increase in the microvascular flow index at the conclusion of the 6-h study period (2.6 ± 0.6 vs. 2.0 ± 0.5, $P < 0.05$). However, some studies (43) have indicated that the combination of TP and NE does not improve microcirculation, suggesting that microcirculation is primarily influenced by factors such as patient volume status, resuscitation duration, and disease progression. The latest guidelines from the "Rescuing Sepsis Campaign" emphasize the importance of relying on microcirculation to guide resuscitation strategies, necessitating adjustments to existing treatment approaches and aiming for more accurate clinical predictions (44). The inconsistent results reported in the aforementioned studies can be attributed to variations in study subjects, conditions for evaluating microcirculation, and strategies used for TP infusion (45,46). The improvement of microcirculation perfusion by TP and its underlying mechanisms pose challenging questions that require further experimental investigations for resolution.

Disadvantages of TP

Indeed, the clinical use of TP has been associated with several problems and adverse reactions. Common adverse effects include gastrointestinal reactions, electrolyte disturbances, cardiovascular events, and respiratory adverse events. Gastrointestinal adverse effects such as nausea, abdominal pain, and diarrhea are frequently observed with TP administration. Electrolyte disturbances are linked to TP's antidiuretic effect through the activation of V2 receptors. Cardiac arrhythmias and myocardial ischemia are the most common cardiovascular adverse effects. Respiratory adverse effects may include dyspnea (47). In addition, there have been reports of rare cases of ischemic skin necrosis after TP usage (48–51).

Regarding the question of whether the combination of NE and TP improves survival compared with NE alone, the studies included in our analysis suggest a potential improvement in 7-day survival. However, there does not seem to be a significant improvement in 28-day mortality.

These findings highlight the importance of considering the potential adverse effects and limitations associated with TP use in clinical practice. Health care professionals should closely monitor patients for any adverse reactions and weigh the potential benefits against the potential risks when using TP. Further research and evidence are needed to better understand the overall impact of TP on survival outcomes.

Limitations of this review

This review acknowledges several limitations that should be considered. First, the included trials spanned a long period, ranging from before 2008 to the latest publication in 2022. During this time, advancements have been made in the early identification of sepsis and early goal-directed therapy, which may affect the comparability of the studies. Second, because of significant heterogeneity among the included experiments and the limited number of studies, a quantitative meta-analysis could not be conducted. Third, it is important to recognize that the included studies were small and susceptible to bias. The number of clinical trials comparing TP combined with NE to NE alone is relatively limited, and there is a lack of large-scale, multicenter, double-blind clinical trials. One of the main reasons for this scarcity of research may be the gradual shift in attention toward vasopressin as a treatment option. However, our team reviewed data from the National Food and Drug Administration of several densely populated developing countries, including China and India, and found that vasopressin has not been approved for use in any of these countries. In addition, vasopressin does not seem to improve 28-day mortality and may impose a greater economic burden on patients. Finally, large-scale, multicenter, double-blind clinical trials are necessary to further support and validate the observations made in this review.

CONCLUSIONS

For patients with septic shock, the use of NE in combination with a small dose of TP in the early stage is a feasible approach. This treatment strategy has shown potential benefits, including reducing the dosage of NE, decreasing lactate levels, lowering HR, and improving renal function while achieving the target MAP. However, it is important to be mindful of the potential risk of adverse reactions. Careful monitoring of the patient's overall condition and the possibility of extremity skin ischemia is crucial during medication.

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